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Drug Addiction as a "Physical Disease:"
The Role of Physical Dependence
and other Chronic Drug-Induced
Neurophysiological Changes in
Compulsive Drug Self-Administration

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Abstract

Physical-dependence-based theories of addiction regard compulsive drug taking as the behavioral manifestation of a desperate need to relieve aversive autonomic withdrawal symptoms. In the present article, the withdrawal-relief paradigm, or opiate model of addiction, is critically examined in the light of recent experimental and clinical evidence for various addictive drugs. It is concluded that contrary to the opiate model, the constellation of pathological behaviors defining addiction (compulsive drug use, craving, loss of control, and a persistent tendency to relapse) does not primarily reflect a need to relieve actual or conditioned autonomic withdrawal symptoms. Recent theories of addiction emphasize the positive reinforcing properties of drugs and sensitization of brain dopamine systems rather than negative reinforcement or drug-opposing neuroadaptations. Despite the failure of the opiate model, recent evidence suggests that persistent drug-induced changes in the physical brain may underlie addictive behavior, consistent with the general notion of addiction as a physical disease.

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Throughout much of this century, addictive behavior was popularly understood in terms of a withdrawal-relief model that was largely based on the American experience with opium derivatives. Chronic use of opiates such as heroin or morphine causes obvious pathological changes in autonomic functioning which are temporarily alleviated by more opiate; hence it was assumed that addicts' compulsive drug use was motivated by a desperate need to maintain a more-or-less normal physiological state. This "physical dependence" constituted "true addiction" according to the traditional view, the "opiate model" of addiction, which has also become identified with the notion that addiction represents a "physical disease." By contrast, compulsive use of drugs such as cocaine or nicotine is not accompanied by obvious signs of physical dependence and was therefore thought to be driven by mere "mental" factors such as pleasure-seeking, escapism, or simply "habit." This type of drug use was termed "psychological" dependence and was regarded as far less serious and intransigent than "physical" dependence. Even cocaine was considered nonaddictive on the basis of this (until recently) widely held view of addictive behavior (Jones, 1992; Van Dyck & Byck, 1982; Withers, Pulvirenti, Koob & Gillin, 1995).

In the past decade there has been a major paradigm shift away from the traditional emphasis on physical dependence as the _sine qua non_ of addiction. This sea change was reflected in the diagnostic criteria of addictions in the revised DSM-III (American Psychiatric Association, 1987) and the ICD-10 (WHO, 1993), both of which de-emphasized physical dependence compared to earlier versions. Behavioral and self-report criteria such as compulsive use, drug craving, and loss of control over drug use are now commonly regarded as the essential defining features of addictions (Cottler et al., 1995;

Gossop et al., 1995; Jaffe, 1992; Miller, Gold & Stennie, 1995; Orford, 1985; Roache & Meisch, 1995; Robinson & Berridge, 1993; Rounsaville, 1995; Self & Nestler, 1995; West & Gossop, 1994; Wise & Bozarth, 1987; Wolffgram & Heyne, 1995). The impetus for the paradigm shift came in part from the findings of animal studies of drug reinforcement and brain reward circuits, but also from the recent American epidemic of cocaine addiction and from widespread recognition of nicotine as an addictive drug. At present, physical dependence seems rather peripheral to the issues currently addressed by addiction researchers, and one may be tempted to ask, does physical dependence play a primary motivational role in addictive behavior? Or is it simply a kind of side effect of chronic abuse of depressant drugs, like cirrhosis of the liver in alcoholics? The present paper addresses these questions by reviewing two of the more influential withdrawal-relief theories of addiction and evidence pertaining to them. Recent findings weigh against traditional conceptions of addiction in which aversive autonomic changes play a major role in compulsive drug use; however, the currently popular view that addictive behavior results from chronic drug-induced pathological changes in dopaminergic brain circuits is certainly consistent with the general notion of addiction as a "physical disease" (for an excellent discussion of the rationale for classifying addictive disorders as "disease," see Maltzman, 1994).

Opiate Addiction: Wikler's Theory

Abraham Wikler developed a highly influential theory of opiate addiction based on research spanning several decades. The rationale for emphasizing physical dependence as the core feature of addiction was stated by Wikler (1980) in a book summarizing his work, *Opioid Dependence*: "It would seem that the main distinction between psychic and physical dependence is that the former is a vaguely defined cluster of inferences derived from the subjective reports of the subject, while the latter is inferred from objective changes in his autonomic nervous system and behavior" (p. 25). According to Wikler, "Distressing drug-withdrawal syndromes are promptly alleviated by renewed administration of the drug in question, and it is presumed that such 'need reduction' has powerful, appetitively reinforcing effects" (p. 26). For opiates such as heroin or morphine, continuous administration for a few weeks will lead to withdrawal signs of autonomic hyperactivity which begin several hours after the last dose and generally subside within a week. The most common symptoms are diarrhea, tremor, rhinorrhea, lacrimation, mydriasis, chills, sweating, tachycardia, nausea, anorexia, and hyperthermia. Wikler also included self-reported "craving" as a withdrawal symptom because he assumed that it reflected an intense need to relieve the distressing autonomic symptoms.

Wikler himself noted two crucial problems for the withdrawal-relief theory of opiate addiction and attempted to resolve them. One was that the model cannot explain why an addict would have taken opiates so regularly and in such quantity to become physically dependent in the first place. A popular view is that the pleasureable effects of a drug such as heroin provide the initial motivation for repeated, voluntary use; only after physical dependence develops is the user "hooked." But Wikler minimized the role of drug-induced euphoria in the acquisition of an opiate habit, noting that first-time use of heroin

more often results in dysphoric effects such as nausea and dizziness than euphoria. According to Wikler (1980), "In the United States, the vast majority of opioid addicts begin and continue their use of the drug (usually heroin) by self-injection in imitation of their drug using peers in the "street corner society'" (p. 28). Wikler (1977) further hypothesized that even a single injection of heroin induces physical dependence. Thus, after the first dose, repetition of drug-taking has a rewarding effect because it alleviates "covert abstinence changes" (p. 36), a "subclinical" withdrawal syndrome consisting of adverse symptoms which are too subtle to be detected externally (Wikler, 1980). However, Bozarth and Wise (1983, 1984) have demonstrated that a single injection of heroin is reinforcing in drug-naive rats, inducing a clear preference for the environment in which the effects of the drug were experienced ("place preference"). As the very first dose of heroin cannot possibly have any withdrawal-relieving effect, "subclinical" withdrawal relief was ruled out in their experiment. Of course, numerous animal studies have clearly established that opiates such as heroin and morphine are powerfully reinforcing in the absence of any detectable physical dependence (Bozarth, 1994; Koob, 1992; Schuster & Woods, 1968; Stewart, de Wit & Eikelboom, 1984).

The second problem addressed by Wikler was the evident inability of the withdrawal-relief model to account for relapse following subsidence of the withdrawal syndrome. Wikler (1977, 1980) noted that the vast majority of opiate addicts in drug-treatment programs relapse within a year of detoxification, regardless of the type of treatment employed. But detoxified addicts are by definition no longer physically dependent; why would they relapse to addiction if they no longer required the withdrawal-relieving effects of opiates? Wikler's solution was to propose that withdrawal symptoms become classically conditioned to the environment in which a junkie hustles for and self-administers opiates. Wikler described anecdotal reports of addicts experiencing flu-like symptoms when they returned to drug-associated home environments following inpatient detoxification. Such conditioned responses (CRs) cannot be extinguished by merely removing the addict from the drug-associated environment to jail or hospital for detoxification, for when the detoxified addict is released and returns home, conditioned withdrawal symptoms are elicited which demand relief ("craving"), reinstating the cycle of addictive behavior.

Wikler (1977, 1980) was able to demonstrate that opiate withdrawal symptoms could be conditioned to a distinctive environment in which they repeatedly took place. Rats that underwent repeated morphine withdrawal in a distinctive cage continued to display withdrawal signs such as "wet-dog shakes" when placed in the same environment for up to 155 days after the last dose of morphine. But in Wikler's experiments the distinctive cage was always experienced by the physically dependent rats in a withdrawal state rather than an intoxicated state. Wikler thus did not show that drug-associated stimuli specifically evoke drug-opposite or withdrawal symptoms instead of drug-like symptoms. O'Brien, Ehrman and Ternes (1984) described a similar experiment in which withdrawal-inducing injections of the opiate antagonist naloxone were repeatedly given to methadone patients in the presence of distinctive cues. When a saline injection was subsequently given in the presence of the same cues, conditioned withdrawal symptoms were evoked.

But the distinctive cues that acted as conditioned stimuli (CSs) had been consistently paired with opiate withdrawal and not with opiate intoxication. In real-life situations experienced by opiate addicts, drug-related stimuli are repeatedly paired with *both* intoxication and withdrawal, leaving open the possibility that drug-like responses could become conditioned to such stimuli in addition to, or instead of, withdrawal-like responses.

Siegel (1977) proposed that the unconditioned response to opiate administration is compensatory, i.e., it opposes the direct effect of the drug. Therefore any stimuli associated with drug administration which can reliably predict the unconditioned stimulus of pharmacological activity can serve as CSs capable of eliciting compensatory CRs. Siegel's experiments indicated that exposure of previously morphine-injected, tolerant rats to drug-administration rituals in the form of a saline injection elicited an apparent hyperalgesic response which Siegel interpreted as the unmasked compensatory CR subserving tolerance. In other words, according to Siegel, only drug-opposite responses become conditioned to drug-associated cues. Eikelboom and Stewart (1982) however pointed out that the apparent "hyperalgesia" observed by Siegel could be explained by conditioning of the morphine-induced increase in locomotor activity, a direct drug effect rather than a compensatory CR. In contrast to Siegel, they found that the direct autonomic and behavioral effects of morphine are readily conditioned to drug-associated cues and that such CRs can even reverse withdrawal symptoms. Moreover, stimuli paired with morphine injections readily acquire secondary reinforcing properties (Carroll & Comer, 1996). O'Brien et al. (1984) described how heroin addicts who were allowed to "shoot up" with saline reported typical heroin euphoria and "rush," and opiate-like physical effects were clearly observed. Such conditioned drug effects were extinguished after a few saline trials. It is now well-established that drug-like effects can be elicited in opiate addicts by presentation of drug-related CSs, and that such effects are usually accompanied by drug craving (Childress, McLellan & O'Brien, 1985; Powell, Bradley & Gray, 1992).

Recent work has elucidated the distinctive properties of drug-like and withdrawal-like responses to drug cues. In detoxified opiate addicts, repeated exposure to drug-related cues without drug reinforcement results in rapid extinction of opiate-like responses, whereas withdrawal-like physiological responses and craving are relatively resistant to extinction (Childress, McLellan, Ehrman & O'Brien, 1988; O'Brien, Childress, McClellan and Ehrman, 1992; Powell et al., 1992). This would seem to support Wikler's idea that, long after detoxification, drug-related cues elicit conditioned withdrawal symptoms which demand relief and thus induce drug craving. However, although subjective craving seems to be a virtually universal response of opiate addicts to drug cues, withdrawal-like responses are not. A substantial minority of opiate addicts deny experiencing any subjective withdrawal sickness in the presence of such cues, with some reporting drug-like effects or no effects other than craving (Childress et al., 1988; Powell et al., 1992). Moreover, physiological responses described as "withdrawal-like" in opiate addicts (e.g., increases in heart rate and sweating, and decreases in skin temperature) were also reliably triggered by cocaine-related cues in detoxified cocaine addicts, in which case the responses were termed "drug-like" because they resembled the direct stimulant effects

of cocaine (O'Brien et al., 1992). One interpretation is that cocaine supports drug-like conditioning while opiates support drug-opposite conditioning. But this idea contradicts Wikler's theory, because the relevant drug cues similarly evoked strong craving whether the addicts were addicted to opiates or cocaine, thus indicating a dissociation of craving from withdrawal-like responding. A more plausible interpretation is that both the supposed "withdrawal-like" responses to opiate cues and the "drug-like" responses to cocaine cues reflect orienting responses (ORs) to significant stimuli (Maltzman, 1979) rather than conditioned withdrawal or conditioned drug effects. The OR is manifested by transient increases in measures of physiological arousal, including increased sweat responses, pupil dilation, heart rate acceleration, and decreased skin temperature. Human subjects display unusually strong ORs to stimuli which have personal significance to them (Wingard & Maltzman, 1980). What could be more personally significant to addicts than stimuli associated with the use of their drug of choice? The cue exposure approach of Childress, O'Brien and their colleagues has been shown to significantly reduce self-reported opiate or cocaine craving, whereas the physiological responses to drug cues are more persistent, supporting the OR interpretation. An increase in nonspecific arousal and craving when exposed to drug cues also characterizes abstinent alcoholics and cigarette smokers (Tiffany, 1990). Physiological arousal may be a universal response of addicts to drug cues, irrespective of the type of drug they were addicted to.

McAuliffe (1982) tested Wikler's conditioned withdrawal theory of relapse by interviewing 40 long-term street addicts who had experienced at least one extended period of abstinence outside of an institution. Only 11 reported ever having experienced withdrawal-like symptoms following subsidence of the acute withdrawal syndrome, and all 11 described the symptoms as mild and rare. Only one subject claimed to have relapsed to addiction as a result. The reasons most often given for relapses reflected a desire for drug-induced euphoria or "high." McAuliffe concluded that drug-associated stimuli and environments evoke a craving for the drug "high" and that this effect accounts for most cases of relapse rather than a need to relieve conditioned withdrawal symptoms. Other studies have documented a variety of attributions given by addicts for their relapses, including negative mood states, unpleasant events, and peer pressure (Cummings, Gordon & Marlatt, 1980; O'Brien, Childress, McLellan, Ternes & Ehrman, 1984). In these studies too, unpleasant physical symptoms were rarely mentioned by addicts as causes of their relapse.

Based on his theory of relapse, Wikler (1980) proposed that temporary use of the opiate antagonist naltrexone would allow opiate addicts to repeatedly experience drug-associated cues and conditioned withdrawal symptoms without the possibility of relief by heroin, leading to extinction of drug-associated CRs, at which point naltrexone could be discontinued. Rawson and Tennant (1984) reported that opiate addicts who took naltrexone for 6 months showed a readdiction rate of more than 90% at 5-year follow-up. It was concluded that although naltrexone protects postaddicts from relapse and reduces craving *while they are taking it*, the antagonist does not reduce relapse rates beyond the treatment period. Wikler's hypothesis that naltrexone "extinction" of conditioned withdrawal would prevent later relapse was not supported. As long as the antagonist is

taken, craving and opiate use are reduced (presumably because opiates are effectively unavailable), but once off naltrexone relapse is just as likely in the long term as it is for postaddicts who had never been treated with naltrexone.

Stewart and her colleagues (Stewart, 1983, 1984; Stewart et al., 1984) proposed an alternative view of opiate relapse. Noting that a single noncontingent "priming" injection of heroin reinstated heroin-reinforced responding following extinction in rats, Stewart et al. suggested that drug-associated stimuli can similarly "prime" heroin relapse by evoking conditioned drug-like effects. Supporting this idea, Stewart (1984) found that stimuli paired with drug effects later acted as primes by reinstating drug-reinforced responding following extinction, just as a shot of heroin itself did. Generalizing these results to human addicts, Stewart et al. concluded that stimuli such as drug-using friends and the settings in which drugs were taken act as persistent goads to further drug-taking by reminding addicts of pleasureable drug experiences. Consistent with the priming theory, postaddicts have described how craving was triggered by drug-associated social settings or other drug-related stimuli during the early months of heroin abstinence (Waldorf, 1983), and craving for heroin can be powerfully triggered by heroin itself (Meyer & Mirin, 1979). Recently Stewart and Wise (1992) directly pitted the withdrawal-based or opponent-process view of relapse against their priming or "proponent-process" theory in an animal model. Following extinction of heroin-reinforced responding, a priming injection of morphine produced a sustained reinstatement of responding, whereas an injection of naltrexone actually decreased responding below the level of a saline injection. Results contradicted the withdrawal-relief theory, which predicts that drug-opposite states rather than drug-positive states trigger craving and renewed drug intake. Substantial evidence indicates that the priming effects of both drug and nondrug reinforcers are clearly based on their positive reward properties irrespective of deprivation states (de Wit, 1996).

Wikler (1980) included craving as a withdrawal symptom despite its subjective, self-report nature. He distinguished between "purposive abstinence signs" such as craving and drug-seeking behavior, which were cortical in origin (having been eliminated in one physically dependent patient by bilateral prefrontal lobotomy!), and "nonpurposive abstinence signs" of autonomic origin which were not affected by lobotomy in humans nor by complete decortication in dogs. But Wikler's assumption that the craving for opiates reflects a desperate need to relieve distressing autonomic withdrawal symptoms is inconsistent with evidence that craving does not inevitably accompany elicitation of the physiological withdrawal syndrome in opiate addicts, nor does alleviation of autonomic and even affective symptoms of withdrawal by nonopioid drugs necessarily alleviate craving. Kanof et al. (1992) reported that naloxone induced clear autonomic withdrawal signs and a marked increase in dysphoria as measured by the Profile of Mood States (POMS) in methadone patients, yet 18 of the 20 addicts reported no craving for opiates during naloxone-precipitated withdrawal, and craving scores did not differ between placebo and naloxone conditions - results the authors considered "remarkable" (p. 361). It is difficult to imagine that the physiological symptoms of opiate withdrawal could be the basis of craving when such symptoms are generally unspectacular for most opiate addicts

using street heroin, often no worse than a case of influenza (Gossop & Bradley, 1984). Addicts tend to rate craving as the most serious aspect of opiate abstinence, while physicians tend to rate the autonomic changes as the most serious symptoms (Cohen, Klett & Ling, 1983). Autonomic withdrawal changes appear to be largely mediated by rebound hyperactivity of the noradrenergic system, particularly the major noradrenergic nucleus in the brainstem, the locus coeruleus (LC) (Gold & Pottash, 1983; Gossop, 1988; Self & Nestler, 1995; Suzuki, Tsuji, Mori, Misawa & Nagase, 1995). Noradrenergic LC neurons are inhibited by opiates but become tolerant to chronic opiate inhibition and exhibit rebound hyperactivity upon naloxone challenge, resulting in increased sympathetic outflow. These same cells are also activated by conditioned fear stimuli (Abrahamsen, Caldarone, Stock, Schutz & Rosellini, 1995). They can be inhibited by the nonopioid alpha-2 agonists clonidine and lofexidine, which reverse most autonomic withdrawal signs in human opiate addicts and also significantly reduce affective symptoms such as anxiety, irritability and anger (Gold & Pottash, 1983). When physically dependent opiate addicts are given either of these drugs during the height of the withdrawal syndrome, they typically claim they are no longer in withdrawal or "kicking", and after 14 days of treatment the drugs can be withdrawn without re-emergence of symptoms. However, the initial enthusiastic response of many physicians that clonidine and lofexidine represented the long-sought nonaddictive "cure" for opiate addiction has proven to be unfounded. Detoxification with clonidine or lofexidine does potently alleviate withdrawal discomfort, but is rapidly followed by relapse in the majority of cases (75% or more) (Ginzburg, 1983; Gossop, 1988; Kleber, 1983; Kleber et al., 1984). Further, despite the alleviation of autonomic and affective withdrawal signs, craving for opiates is unaffected and generally remains at high levels throughout treatment with clonidine or lofexidine (Rounsaville, Kosten & Kleber, 1985; Rawson, Washton, Resnick & Tennant, 1984). Rawson et al. concluded that relapse during detoxification is triggered by craving for opiates rather than withdrawal symptoms, as the latter but not the former were relieved by clonidine. Indeed, one study found that clonidine was even more effective than morphine at eliminating autonomic withdrawal signs (Jasinski, Johnson & Kocher, 1985), yet the clonidine-treated opiate addicts nevertheless complained about clonidine and requested morphine instead. Jasinski et al. concluded that withdrawal symptoms are not the basis of drug-seeking behavior. Alpha-2-agonists, though useful for alleviating withdrawal symptoms without euphoria during detoxification, do not substitute for opiates and do not reduce relapse rates compared to other detoxification methods.

The central question raised by a critical examination of the withdrawal-relief theory is whether such "need-reduction" does indeed have "powerful, appetitively reinforcing effects" as Wikler (1980, p. 26) proposed. Wikler's own studies purporting to show that physical dependence dramatically increases opioid reinforcement are unconvincing. For example, his finding that physically dependent rats in withdrawal consumed significantly more of an etonitazene solution than did drug-naive rats can be interpreted as reflecting factors such as higher tolerance and greater drug experience in the physically dependent rats rather than withdrawal-relief. Wikler himself noted that both groups of rats drank to the point of overt intoxication, lending support to a tolerance-based interpretation of the

increased consumption by physically dependent rats. Moreover, even nondependent animals consume significantly more etonitazene solution than water (McMillan et al., 1976). Schuster and Villarreal (1968) concluded that escape from withdrawal is not the primary motivation for drug-taking in physically dependent rats, citing a study by Khazan, Weeks and Schroeder which showed that such rats resume lever-pressing for morphine well before any signs of withdrawal appear on EEG or EMG measures. In human opiate addicts, too, the evidence for withdrawal-relief as a major motive for opiate use is not compelling. Opiate addicts typically take far greater doses of drugs than are necessary to relieve withdrawal symptoms (McAuliffe & Gordon, 1974), and given the considerable expense of a heroin habit, this would be wasteful unless it is the intoxication or "high" rather than simply withdrawal-relief that is desired. Similar considerations may explain the clear superiority of high dose over low dose methadone maintenance in reducing heroin use even when the low doses employed are medically sufficient to relieve withdrawal symptoms (Jaffe, 1995; Johns, 1994; Kreek, 1992). Wikler himself described an experiment in which he allowed a heroin addict to self-inject morphine as often as desired for several months. Towards the end of the period of drug availablility, the addict denied any fear of the impending withdrawal syndrome, and elected to inject large doses of morphine right up to the last day rather than reduce the dose gradually to alleviate withdrawal discomfort. This physically dependent addict's drug use was clearly motivated by the opiate "high" rather than relief of withdrawal.

In a discussion of the nature of opiate reinforcement, Schuster and Villarreal (1968) concluded that although morphine is a positive reinforcer in the absence of physical dependence, "morphine's reinforcing efficacy is markedly amplified when animals are undergoing withdrawal" (p. 822). The latter conclusion was based on research by Schuster and his colleagues which showed that, following substitution of saline for previously morphine-reinforced lever-pressing, physically dependent monkeys in withdrawal exhibited high response rates not exhibited by nondependent monkeys that had previously lever-pressed for much lower doses of morphine. The high response rates of the physically dependent monkeys persisted for the duration of the withdrawal syndrome. Responding for food and water reinforcers was markedly depressed during this period, which was interpreted to rule out a nonspecific effect of opiate withdrawal on response rates. However, given that major symptoms of opiate withdrawal include "nausea and vomiting" and "anorexia" (Schuster & Villarreal, p. 820), one would expect that responses for food and water would be selectively depressed in animals undergoing opiate withdrawal. This leaves open the possibility that the withdrawal state of CNS hyperactivity may have nonspecifically increased response rates for non-gustatory rewards, including drug injections. It should also be noted that the factor of drug experience - or in this case, experience with different dosage levels of differential reinforcement efficacy - was necessarily confounded with the induction of physical dependence in these studies, an issue which will be addressed in more detail below in the context of animal models of alcoholism.

Nonaddict medical patients who receive chronic high doses of potent opiates to the point of physical dependence usually express no desire for more drugs when opiates are

discontinued (Burglass & Shaffer, 1984; Chapman & Hill, 1989; Porter & Jick, 1980; Sellman, Kendall & MacLeod, 1995). Schuster, Greenwald, Johanson and Heishman (1995) recently described how methadone patients who underwent naloxone-precipitated withdrawal for experimental purposes actually refused the offer of methadone to relieve their acute withdrawal distress. Such examples show that drug-seeking behavior is not a necessary consequence of the opiate withdrawal syndrome, a point also supported by studies of certain opioids with mixed actions. Chronic adminstration of the noneuphoriant mixed opioids nalorphine, cyclazocine or butorphanol led to a typically unpleasant opiate abstinence syndrome in human postaddict subjects when the drugs were stopped, but in no case did subjects experiencing withdrawal express a desire for more of these drugs (Pachter & Evens, 1984; Wikler, 1980). By contrast, human postaddicts and laboratory animals readily initiate and maintain self-administration of the mixed opioid buprenorphine as they do for classic opiates such as morphine or heroin, even though chronic use of buprenorphine does not lead to significant physical dependence, and the drug's partial antagonist action precipitates withdrawal symptoms in animals or humans dependent on other opioids (Lewis, Rance & Sanger, 1983; Lukas, Griffiths & Brady, 1983; Woods & Gmerek, 1985). In human postaddicts, buprenorphine is identified as an opiate and produces morphine-like euphoria, but physical dependence is relatively minor even after more than a month of chronic high-dose adminstration (Lewis et al., 1983; Mello, Bree & Mendelson, 1984; Mello & Mendelson, 1984). Although buprenorphine withdrawal is generally quite mild compared to other opioids, buprenorphine has been widely abused in countries where it was readily available (Bickel & Amass, 1995). Lewis (1984) dismissed reports of buprenorphine abuse by opiate addicts as reflecting mere "psychological" dependence because the drug does not produce physical dependence to the degree of other opioids. Buprenorphine is now regarded as a viable alternative to methadone for maintenance treatment of opiate addicts, as it produces agonist effects that addicts like without significant physical dependence or risk of dangerous respiratory depression in overdose (Bickel & Amass, 1995; Jaffe, 1995; Parran, Adelman & Jasinksi, 1994; Strain, Stitzer, Liebson & Bigelow, 1994), although it can precipitate withdrawal and dysphoric effects in patients maintained on high doses of methadone (Walsh et al., 1995).

According to Bozarth and Wise (1983, 1984), the brain substrates of opiate reward and physical dependence are anatomically distinct in the rat. The ventral tegmental area (VTA) supported self-administration of direct morphine infusions, but chronic infusion of morphine into the VTA followed by naloxone challenge yielded no signs of physical dependence. On the other hand, chronic infusion of morphine into the periacqueductal gray (PAG) followed by naloxone challenge produced typical morphine withdrawal signs such as teeth chattering and "wet-dog shakes," but the PAG did not support morphine self-administration. Different sites of action presumably account for the fact that some synthetic opioids can produce physical dependence without reinforcement, whereas others are reinforcing yet fail to produce major physical dependence. Such dissociation of opiate reinforcement from physical dependence is inconsistent with physical dependence-based explanations of opiate addiction. More recently, however, there have emerged indications of some degree of interaction between brain substrates of physical dependence and opiate

reinforcement. Harris and Aston-Jones (1994) reported that microinjection of direct dopamine agonists into the nucleus accumbens attenuated morphine withdrawal signs, whereas dopamine antagonists precipitated withdrawal signs at the same site in morphine-dependent rats. The nucleus accumbens is one of the terminal fields of VTA neurons and is thought to be crucial for the positive reinforcing actions of opiates and other addictive drugs (Di Chiara, 1995). Harris and Aston-Jones noted that although the nucleus accumbens is probably not a major site mediating opiate withdrawal symptoms, it has connections with other brain regions known to be important in opiate withdrawal and may therefore play a modulatory role. Corrigal and Vaccarrino (1988) found that microinjection of an opiate antagonist into either the nucleus accumbens or the PAG caused a compensatory increase in heroin-reinforced responding. They concluded that the PAG may mediate some of the discriminative stimulus properties of opiates in addition to its role as a brain site of physical dependence. Morphine microinjection into this region did not, however, reinstate heroin-reinforced responding in Stewart's (1984) "priming" paradigm, whereas morphine microinjection into the VTA did do so. As noted previously above, the priming effect of drugs is based on their positive reinforcing properties irrespective of deprivation states (de Wit, 1996).

Wikler (1980) described how hospitalized opiate addicts would try to "con" him into giving them morphine by mimicking withdrawal symptoms. The fact that Wikler's addicts would do this is not surprising given Wikler's view that opiate use is primarily motivated by a need to relieve withdrawal sickness. On the other hand, some studies assessing addicts' own justifications for their chronic use of opiates have found that desire for euphoria was the main self-reported motive for continued heroin use rather than relief of withdrawal symptoms (McAuliffe & Gordon, 1974; McAuliffe, Rohman, Feldman & Launer, 1985). This may explain why cocaine is reportedly used as a substitute for heroin by many physically dependent heroin addicts when opiates are unavailable (Hunt, Lipton, Goldsmith & Strug, 1983; Kreek, 1992). Such behavior is inexplicable from the standpoint of the withdrawal-relief theory because the catecholamine reuptake-blocking action of cocaine powerfully increases rather than decreases noradrenergic activity and autonomic arousal. On the other hand, cocaine is a potent euphoriant which stimulates the same dopaminergic "reward" pathway in the brain as heroin (Kornetsky & Porrino, 1992; Sarkar, Huston-Lyons & Kornetsky, 1995; Wise & Rompre, 1989), perhaps accounting for the substitution of cocaine for heroin despite its opposite autonomic effects. In summary, then, the withdrawal-relief theory of opiate addiction championed by Wikler, and once so widely accepted, is clearly not supported by most recent evidence. To paraphrase Wise and Bozarth (1987), physical dependence seems neither necessary nor sufficient for opiate addiction. As Self and Nestler (1995) concluded, "motivational symptoms of opiate addiction can develop independently of, and perhaps even more readily than, physical symptoms of opiate dependence" (p. 485). Compulsive use of opiates such as heroin - the traditional example *par excellence* of the very concept of addiction as a desperate physical need to relieve pathological autonomic symptoms - evidently requires an alternative account.

Jellinek's Disease Model of Alcoholism

E.M. Jellinek (1960) essentially applied the opiate model to alcoholism in his influential book, *The Disease Concept of Alcoholism*. Jellinek clearly regarded alcoholism as a "disease" only when physical dependence was present. This "medical" or "disease" model of alcoholism followed an earlier "disease" conception put forward by Jellinek (1952) in which the critical symptom of "alcohol addiction" was loss of control over alcohol intake. According to Jellinek (1952), "The disease conception of alcohol addiction does not apply to the excessive drinking, but solely to the 'loss of control' which occurs only in one group of alcoholics and then only after many years of excessive drinking" (p. 674). Jellinek defined "loss of control" in the following manner:

> Loss of control means that any drinking of alcohol starts a chain reaction which is felt by the drinker as a physical demand for alcohol. This state, possibly a conversion phenomenon, may take hours or weeks for its full development; it lasts until the drinker is too intoxicated or too sick to ingest more alcohol (p. 679).

Further:

> The 'loss of control' is effective after the individual has started drinking, but it does not give rise to a new drinking bout. The drinker has lost the ability to control the quantity once he has started, but he can still control whether he will drink on any given occasion or not (p. 680).

Thus the drinking pattern of the "alcohol addict" often takes the form of prolonged drunken binges or "benders," followed by periods of abstinence lasting days or weeks ("going on the water wagon"), during what Jellinek called the "crucial phase" of alcoholism. Although Jellinek described withdrawal-relief drinking as occurring in the subsequent "chronic phase," it was assigned relatively little importance, an effect of chronic heavy drinking (along with other symptoms such as ethical deterioration, impairment of thinking, and loss of alcohol tolerance) rather than cause: "The effects of prolonged heavy drinking on the organism may occur in the nonaddictive alcoholic too; even delirium tremens may develop" (p. 684). Thus physical dependence was not a defining feature of "alcohol addiction" as originally defined by Jellinek (1952). Rather, the essential symptom was "loss of control."

Jellinek (1960) subsequently revised his "disease" conception of alcoholism such that it corresponded to the widely accepted withdrawal-relief theory of opiate addiction. The withdrawal syndrome which develops after chronic use of alcohol or other sedative drugs typically includes many of the autonomic symptoms of opiate withdrawal, but can be far more dangerous due to the additional possibility of delirium tremens and epileptiform seizures (Kaufman, Shaffer & Burglass, 1984). Jellinek therefore reserved terms such as "true drug addiction" (p. 121) and "true disease processes" (p. 111) for only two forms of alcoholism which he called gamma and delta. Of the first type, Jellinek (1960) wrote:

> Gamma alcoholism means that species of alcoholism in which (1) acquired tissue tolerance to alcohol, (2) adaptive cell metabolism, (3) withdrawal symptoms and "craving," i.e., physical dependence, and (4) loss of control are involved (p. 37).

Like Wikler, Jellinek assumed an automatic link between withdrawal symptoms and craving, such that the former necessitated the latter:

> It (gamma alcoholism) is what members of Alcoholics Anonymous
> recognize as alcoholism to the exclusion of all other species. Of course
> they use loss of control and 'craving' as the criteria *par excellence* but
> these necessarily involve the other characteristics of gamma alcoholism
> (tolerance and withdrawal symptoms) mentioned above (p. 38).

Alcohol addiction was manifested differently in delta alcoholism, which has the first three characteristics of the gamma species (i.e., physical dependence) but "loss of control" is replaced by "inability to abstain," i.e., the necessity of withdrawal-relief drinking due to the emergence of withdrawal symptoms whenever blood alcohol levels are low. Jellinek wrote that the delta type of alcoholism mainly occurs in countries such as France where heavy overall daily consumption of alcohol is culturally accepted and encouraged. Small, nonintoxicating amounts of alcohol are consumed steadily over the waking hours of each day, and physical dependence ensues after many years of such drinking. However, unlike the gamma type, craving was not the usual motive for drinking in the delta alcoholic; rather, "The incentive to high intake may be found in the general acceptance of the society to which the drinker belongs" (p. 38). Nevertheless,

> ...it is the adaptation of cell metabolism, and acquired increased tissue
> tolerance and withdrawal symptoms, which bring about "craving" and
> loss of control or inability to abstain (p. 40).

Jellinek suggested that "the metabolism of nervous tissue cells becomes conditioned by the 'signal' of the 'first drink'" (p. 149) as a withdrawal-based explanation of loss of control . Further,

> ...it may be said that an "overpowering desire," i.e., a physical dependence
> upon alcohol, is shown only in the presence of withdrawal symptoms, and
> these are late developments in gamma and delta alcoholism (p. 43).

Jellinek (1960) claimed that such craving was directed not at alcohol *per se*, but at "relief from the painful withdrawal symptoms" (p. 146). Thus Jellinek was at pains to explain why the gamma alcoholic, though physically dependent, could abstain for days or weeks between benders. During that time, withdrawal symptoms should elicit craving. Unlike Wikler however, Jellinek admitted that physical dependence could not account for the common phenomenon of relapse following subsidence of the abstinence syndrome, nor could it explain the years of heavy drinking that led to physical dependence in the first place (p. 146). Compulsive drinking for many years in the absence of withdrawal symptoms, even when there was concomitant damage to family, employment, socioeconomic status, brain, and liver, was regarded by Jellinek as motivated entirely by psychological factors and hence did not constitute "legitimate" addiction in his view (p. 70).

Jellinek (1960) nevertheless predicted that animal models of physical dependence upon alcohol would support his withdrawal-based theory of alcohol addiction. He was wrong. Despite extensive efforts by numerous researchers in many different laboratories, withdrawal-relief drinking has proven extremely difficult to demonstrate in laboratory animals. Even rats rendered severely physically dependent due to chronic forced ethanol intake usually display an aversion to the effects of ethanol (LeMagnen & Marfaing-Jallat, 1984), and when they occasionally do not, their voluntary ethanol intake can often be

attributed to simple tolerance to the aversive effects of ethanol rather than withdrawal-relief (Cappell & LeBlanc, 1983). For example, rats can be induced to drink ethanol solutions to the point of physical dependence under schedule-induced polydipsia conditions (Falk, Samson & Winger, 1972; Falk, 1983; Tang, Kenny & Falk, 1984). However, when the inducing schedule is removed, the physically dependent rats immediately reduce their ethanol intake to the level of control animals despite the presence of withdrawal symptoms and the repeated experience of withdrawal-relief by ethanol. Another approach (Marfaing-Jallat & LeMagnen, 1982; LeMagnen & Marfaing-Jallat, 1984; Marfaing-Jallat & LeMagnen, 1985) rendered rats physically dependent by chronic forced infusions of ethanol, then made an ethanol solution or water the only available fluid for 8 hours/day on alternating days (i.e., ethanol, then water, then ethanol, etc.). This procedure maximized withdrawal symptom severity when the ethanol solution was presented. Under these conditions, physically dependent rats consumed significantly more ethanol solution than did nondependent controls, but the difference could be attributed to tolerance. The physically dependent rats consumed no more of the ethanol solution than water, thus apparently satisfying thirst, whereas the nondependent rats consumed less ethanol solution than water. However, in other studies LeMagnen and colleagues did get physically dependent rats to consume more ethanol solution than water (LeMagnen, Marfaing-Jallat, Diot and Dossevi, 1984; Marfaing-Jallat, Miceli & LeMagnen, 1983), ruling out a tolerance-based interpretation for those specific experiments. Yet even those results did not make a strong case for withdrawal-relief drinking. Naloxone reduced ethanol intake to the level of water intake in physically dependent rats and markedly reduced ethanol intake in ethanol-naive rats, suggesting that sensitization to the primary rewarding effects of ethanol may have been responsible for the increased ethanol consumption by physically dependent rats, given the evidence for endogenous opioid involvement in alcohol primary reward (Berman, Lee, Olson & Goldman, 1984; Cooper, 1983; de Witte, 1984; O'Brien, 1994; Volpicelli, Alterman, Hayashida & O'Brien, 1992; Volpicelli, Clay, Watson & Volpicelli, 1995). Rewarding effects of ethanol cannot be demonstrated in ethanol-naive rats in the intravenous drug self-administration or place preference paradigms commonly used to assess the reinforcement potential of drugs (Asin, Wirtshaftre & Tabakoff, 1985; Numan, Naparzewska & Adler, 1984). But Reid, Hunter, Beaman and Hubbell (1985) reported that when rats were forced to consume an ethanol solution as the only available fluid for 1 hr/day (followed by water availability for 3 hr/day) for 26 days, place preferences could be demonstrated for ethanol injections administered 35 days after termination of ethanol drinking. The small daily amounts of ethanol consumed by the rats in that study were far too low to induce physical dependence. Thus, some degree of experience with ethanol intoxication can render it rewarding in rats, irrespective of physical dependence.

Wolffgramm and Heyne (1995) gave rats simultaneous free access to several ethanol solutions of different strengths and water for 42 weeks. The rats required 2 weeks of "drug experience" with the ethanol solutions before they settled into a stable pattern of "voluntary" ethanol self-administration which persisted for at least 6 months. During this "controlled use" phase, ethanol intake could be altered by gustatory and social factors. For example, adding quinine to the ethanol solutions dramatically reduced intake,

whereas placing group-housed rats in temporary isolation increased intake substantially; restoration of the original conditions then caused ethanol intake to revert to previous levels. After 42 weeks, however, ethanol intake showed a sustained increase that was no longer so susceptible to environmental changes; it became "irreversible." Adding quinine to ethanol solutions no longer dramatically reduced intake, and changing social conditions failed to modify ethanol intake as well. Further, when ethanol was made available again after 9 months of forced abstinence, ethanol intake increased even beyond pre-abstinence levels - the "alcohol deprivation effect." This was clearly not due to prior physical dependence, as forced chronic administration of nonaversive doses of ethanol to the point of physical dependence actually *reduced* ethanol intake in free choice tests compared to a control condition of intermittent free access to ethanol solutions. Only rats that had self-administered ethanol displayed signs of addictive behavior, i.e., an irreversible increase in ethanol consumption and relapse following an extended period of abstinence. Forced administration leading to physical dependence actually *inhibited* the development of addictive behavior in rats.

It may be argued that the results of rat experiments have little relevance to human behavior compared to studies with primates. In a review of ethanol self-adminstration studies, Cappell and LeBlanc (1983) concluded that the positive reward properties of alcohol are more important than physical dependence in determining the self-administration of ethanol solutions by primates. Like humans, monkeys often show high alcohol consumption in the absence of physical dependence (Mello, Bree, Mendelson & Ellingboe, 1983; Winger & Woods, 1973). The pattern of intake is remarkably similar to that seen for cocaine or amphetamines, consisting of "binges" lasting several days and separated by similar periods of abstinence. With chronic alcohol intake, monkeys often display withdrawal symptoms during the early part of each abstinent period, but only after these symptoms subside do the monkeys resume responding for alcohol. This common finding led Winger, Young and Woods (1983) to propose the "heretical" notion that alcohol withdrawal actually *decreases* the reinforcing effects of alcohol. Supporting this view, Winger (1988) reported that self-administration of intravenous ethanol by physically dependent monkeys was suppressed during withdrawal, such that the more severe the withdrawal symptoms when ethanol was offered, the lower the voluntary ethanol intake. Once withdrawal subsided, Winger's monkeys resumed a high level of ethanol self-adminstration. Mello and Mendelson (1972) described a similar pattern of voluntary alcohol intake in hospitalized, physically dependent human alcoholics. Drunken binges alternated with abstinent periods of 24-36 hr, during which withdrawal symptoms were evident. This is of course what Jellinek (1960) described as gamma alcoholism. It is inconsistent with the withdrawal-relief model, which would predict considerably shorter periods of abstinence given the onset of withdrawal symptoms early in the abstinent period.

Jellinek (1960) assumed that the presence of withdrawal symptoms necessarily entailed "craving" directed at their relief. Ludwig and Stark (1974) investigated craving in hospitalized alcoholics by administering a questionnaire which contained separate subscales assessing craving and withdrawal experiences. The two subscales were

significantly correlated, leading Ludwig and Stark to conclude that withdrawal symptoms underlie craving. However, their craving and withdrawal subscales contained similar items, e.g., questions asking about "nervous" or "anxious" feelings, which probably accounts for some of the shared variance. Like Wikler (1980), Ludwig and Stark justified their emphasis on withdrawal symptoms by stating that craving was an "ephemeral, superfluous construct" unless it could be anchored to its "underlying biological correlates" (p. 904). Alcohol withdrawal, like opiate withdrawal, appears to represent in part a hypernoradrenergic state resulting from overactivity of the locus coeruleus (Dar & Wooles, 1984; Hawley, Major, Schulman & Linnoila, 1985; Manhem, Nilsson, Moberg, Wadstein & Hokfelt, 1985). But although objective and self-report signs of alcohol withdrawal can be effectively relieved by the alpha-2-agonists clonidine and lofexidine, these drugs fail to alleviate craving in alcoholics (Cushman, Forbes, Lerner & Stewart, 1985) as was described previously for opiate addicts. The generalized CNS hyperexcitability that distinguishes alcohol withdrawal from opiate withdrawal is most likely due to neuroadaptations in GABA-A and NMDA receptor systems (Littleton & Little, 1994; Deitrich, Radcliffe & Erwin, 1996); symptoms of this are quite effectively relieved by benzodiazepines, but alcoholics tend to relapse to alcoholism while taking these drugs (Miller, 1995). Thus, effective treatment of withdrawal symptomatology does not appear to reduce craving or likelihood of relapse in alcoholics. In any case the vast majority of alcoholics exhibit only mild to moderate signs of physiological arousal during untreated withdrawal (Miller, 1995).

As with opiate addicts, relapse rates tend to be high by 1 year after detoxification among alcoholics who seek treatment (Orford, 1985). Jellinek (1960) felt that the disease view could not explain relapse because such drinking occurs after the subsidence of the withdrawal syndrome. To account for relapse within the framework of the withdrawal-relief model, Ludwig and Wikler (1974) applied Wikler's conditioned withdrawal-relief theory of opiate relapse to alcoholism. Alcohol-associated cues were said to evoke conditioned withdrawal symptoms, leading to craving for relief and a return to withdrawal-relief drinking in detoxified alcoholics. Craving was presumed to reflect a "subclinical" withdrawal syndrome even when objective autonomic signs were absent. Thus detoxified alcoholics tend to report craving in the presence of alcohol-associated cues, such as the sight of a tavern, alcohol consumption by others, or a bottle of their preferred liquor (Eriksen & Gotestam, 1984; Ludwig, Wikler & Stark, 1974). But as in opiate addiction, the attribution of such craving to conditioned withdrawal symptoms - even of a "subclinical" nature - requires that drug-associated cues support conditioning of drug-opposite or withdrawal symptoms rather than direct drug effects, an idea for which there is only mixed experimental support. Tolerance to ethanol-induced hypothermia has been interpreted as reflecting a conditioned compensatory response of hyperthermia evoked by cues associated with ethanol administration (Crowell, Hinson & Siegel, 1981; Le, Poulos & Cappell, 1979; Mansfield & Cunningham, 1980). According to this view, because the hyperthermia elicited by alcohol-related cues is opposite to the direct action of alcohol, it represents a drug-opposite or withdrawal-like response to alcohol cues, consistent with Ludwig and Wikler's (1974) model of alcoholic relapse. But Maltzman and Marinkovic (1996) have convincingly argued that the apparent compensatory

response of hyperthermia in the presence of alcohol cues was simply an artifact of the testing situation and not a true drug-opposite CR. Moreover, Eikelboom and Stewart's (1982) analysis of the classical conditioning model as applied to drug effects indicated that drug-opposite conditioning should only occur for drug actions on the efferent arm of the CNS, which are opposed by homeostatic mechanisms. An afferent site of drug action, on the other hand, should support conditioning of direct drug effects rather than compensatory responses. As a possible example of this, Kaplan, Meyer and Stroebel (1983a, b) found that 6 of 8 alcoholic subjects who consumed dealcoholized beers rated the drinks as containing alcohol, compared to only 2 of 8 nonalcoholic controls. Placebo intoxication increased alcoholics' ratings of their desire to drink, just as alcohol itself did. Thus alcohol-related cues such as the sight, taste and smell of beer (and probably the expectation of it as well) apparently elicited a conditioned drug-like subjective response and stimulated the desire to drink in alcoholics. Such findings, as well as results of other much-discussed studies in which alcohol-related cues and expectancies increased subsequent drinking behavior (Marlatt, Deming & Reid, 1973; Stockwell, Hodgson, Rankin & Taylor, 1982), are consistent with the "priming" model of relapse proposed by Stewart and associates (Stewart, 1983, 1984; Stewart et al., 1984). According to Stewart et al., drug-related cues evoke conditioned drug-like effects which can "prime" a return to drug-taking. The priming effect can readily explain why alcohol-related cues tend to evoke craving in alcoholics, without appealing to conditioned withdrawal symptoms. Indeed, alcoholics themselves rarely if ever attribute relapse to physical symptoms. The usual self-reported causes of relapse are negative emotional states induced by external life events (Cummings, Gordon & Marlatt, 1980), as Jellinek (1960) had earlier claimed. However, some recent evidence suggests that alcoholics' attributions of relapse to dysphoric states may be post-hoc rationalizations, and that negative mood states do *not* immediately precede alcoholic relapse but rather occur as a *consequence* of relapse (see Maltzman, 1994). There is also considerable evidence for a role of positive or euphoric mood states in alcoholic relapse (Litman, Stapleton, Oppenheim, Peleg & Jackson, 1983; Orford, 1985), consistent with Stewart et al.'s priming model.

Also consistent with the notion of "priming" is Jellinek's (1952, 1960) assertion that the gamma alcoholic experiences the most intense craving not during the height of withdrawal, but when consuming alcoholic beverages - the "loss of control." Just as a noncontingent priming injection of heroin reinstated heroin-reinforced responding following extinction in Stewart's (1983, 1984) rats, the "first drink" can trigger increases in alcohol-reinforced responding and self-reported craving or desire for alcohol in detoxified alcoholics (Ludwig & Wikler, 1974; Stockwell et al., 1982) and even in nonalcoholic social drinkers (Chutuape, Mitchell & de Wit, 1994). In alcoholics, a single drink may in some circumstances act in a manner analogous to electrical stimulation of reward pathways in the brain (ESB), which elicits continuous bar-pressing for further stimulation in laboratory animals. The reinforcing effects of ESB, opiates, cocaine and amphetamines are dependent upon facilitation of dopamine neurotransmission in the mesolimbic dopamine system (Koob, 1992; Sarker, Huston-Lyons & Kornetsky, 1995; Self & Nestler, 1995; Wise & Munn, 1993; Wise & Rompre, 1989; Withers et al., 1995), which is also an effect of low doses of alcohol (Gessa, Muntoni, Collu, Vargiu & Mereu,

1985). All of the above drugs, including alcohol, lower ESB reward thresholds (Kornetsky & Porrino, 1992). In human alcoholics, alcohol consumption and self-reported alcohol-induced craving and loss of control are reduced by pretreatment with dopamine antagonists (Modell, Mountz, Glaser & Lee, 1993). Further, the opiate antagonist naltrexone reduces alcohol euphoria and lowers relapse rates in alcoholics, apparently by reducing the priming effect of "slips" in which the abstinent alcoholic samples a drink (Volpicelli et al., 1995). Sons of alcoholics appear to be relatively more sensitive to the euphoriant or primary rewarding effects of alcohol than sons of nonalcoholics, which may account for the greater vulnerability to alcoholism of the former group (Newlin & Thomson, 1990). Taken together, recent evidence thus suggests that the positive reinforcing properties of alcohol, irrespective of physical dependence, constitutes the basis of compulsive alcohol self-administration, craving, loss of control, and relapse, as appears to be the case for other drug addictions. Correlations between severity of withdrawal symptoms and factors such as quantity and frequency of alcohol intake, craving, and priming effects in human alcoholics have been interpreted as supporting the withdrawal-relief model (Stockwell, 1994). However, the direction of causation may have been misconstrued, such that more severe physical dependence is *caused by* more severe and enduring alcohol habits rather than the other way around. In any case the reported correlations among self-reported craving, physiological variables, and alcohol consumption tend to be small (Tiffany, 1990), arguing against an interpretation of craving and excessive alcohol intake as primarily elicited by actual or conditioned autonomic withdrawal states.

Stockwell (1994) recently suggested that the main force driving compulsive drinking in alcoholics is their need to relieve withdrawal anxiety. The physical manifestations of alcohol withdrawal show a continuum of severity and reflect an underlying aversive anxiety state or "rebound anxiety" (p. 1451), which alcohol ingestion relieves in the short term but amplifies in the long term. Stockwell's view is perhaps better termed a "benzodiazepine model" of alcoholism rather than an opiate model. The benzodiazepines (BZDs) are relevant because these widely prescribed anxiolytic drugs characteristically produce alcohol-like physical dependence and rebound anxiety with regular use, but BZDs rarely become the focus of addictive behavior (King, 1994; Roache & Meisch, 1995; Woods, 1983). Indeed, given the extremely widespread use of BZDs as anxiolytics, muscle relaxants and hypnotics (Gold, Miller, Stennie & Populla-Vardi, 1995) and the close to 100% rate of physical dependence in regular users (Miller, 1995), the withdrawal-relief model would predict a far greater prevalence of BZD addiction than has actually been seen (Ayd, 1983; King, 1994). BZDs are ineffective as reinforcers in normal human volunteers (Woods, 1983; de Wit, Johanson & Uhlenhuth, 1984), and even anxiety patients consistently preferred placebo to diazepam in one study, despite their familiarity with the drug's anxiolytic effects (de Wit, Johanson, Uhlenhuth & McCracken, 1983). Alcoholics and sedative abusers are an exception in that they appear to be more susceptible to BZD reward (Ciraulo et al., 1988; Roache & Meisch, 1995), but their drugs of choice are far more likely to be the focus of abuse and addiction than BZDs (Miller, 1995; Woods, 1983) and are more effective reinforcers in animals and humans (Cappell et al., 1987). In animal studies using high BZD doses, physical dependence

develops rapidly but fails to enhance the weak reinforcing effects of BZDs (Griffiths, Lamb, Ator, Roache & Brady, 1985; Rosenberg & Chiu, 1985). Like alcohol, BZDs potentiate the inhibitory postsynaptic effects of GABA at GABA-A receptors (Lader, 1994), but unlike alcohol and other addictive drugs, BZDs decrease dopaminergic neurotransmission in the mesolimbic dopamine system (Di Chiara, 1995: Wise & Rompre, 1989). As Stockwell proposed for alcohol, regular use of BZDs as anxiolytics does indeed relieve anxiety in the short term but amplify it in the long term, leading to withdrawal or rebound anxiety and initial resistance on the part of some patients to get off BZDs (Cappell et al., 1987; Jaffe, 1992; Miller, 1995). But one could question whether there is true addictive behavior in the sense of compulsive use, craving, loss of control, and a propensity to relapse in most patients who become physically dependent on BZDs. As Roache and Meisch put it, "physical dependence on BZDs may motivate self-medication; however, it does not necessarily produce persistent addictive behavior" (p. 157). Simple advice given by doctors or the media has proven effective in getting many physically dependent BZD users to wean themselves off of these drugs (Gabe, 1994). Using a gradual tapering of the dosage, most physically dependent patients have little difficulty getting off BZDs on their own, and relapse rates are low compared to other drug dependencies (Ashton, 1994). Thus BZDs represent a class of medically useful drugs which, compared to alcohol, are at least as likely to produce physical dependence but which nevertheless represent a relatively minor problem in terms of addiction. By implication, alcoholism in most cases must constitute more than just self-medication of aversive withdrawal symptoms or rebound anxiety. Indeed, physical dependence appears to develop only after many years of alcoholic behavior (Volicer, Volicer & d'Angelo, 1984), as a consequence, not cause, of chronic heavy alcohol consumption.

Psychostimulant Addiction

The resurgence of widespread cocaine abuse in the United States in the 1970s and 1980s was not initially regarded with much alarm. This was because the fallacious view that addiction equals physical dependence was widely held by both the medical profession and the public. Earlier work had clearly shown that chronic cocaine use does not induce physical dependence (see Grinspoon & Balakar, 1985), therefore cocaine was not truly addictive in terms of the opiate model. For this reason the DSM-III (American Psychiatric Association, 1980) did not include cocaine dependence or addiction as a diagnosis, and most medical textbooks did not regard cocaine as addictive for the same reason (Gold & Verebey, 1984). Repetitive use of cocaine was thought to represent mere "psychological" dependence, comparable to binging on potato chips (Van Dyck & Byck, 1982). In other words, cocaine was popularly viewed as a relatively benign illegal drug like marijuana, not even remotely comparable to opiates such as heroin in terms of addiction potential.

As cocaine spread in popularity, reports from users of loss of control over cocaine use and intense cocaine craving became common in the early 1980s (Washton & Tatarsky, 1984). This was a surprising development considering the popular view that cocaine was nonaddictive. The characteristic pattern of cocaine or amphetamine abuse in both humans and laboratory animals takes the form of repeated binges or "runs" of several days,

separated by "crashes" of similar duration in which the user abstains from the drug (Grinspoon & Balakar, 1985; Withers et al., 1995). The fatigue, sleep and depression that occur during the "crash," which some researchers have occasionally referred to as "withdrawal symptoms" (Siegel, 1984; Tennant, 1983; Wikler, 1980), temporarily inhibit further intake of cocaine (Grinspoon & Balakar, 1985; Withers et al, 1995), hence the withdrawal-relief paradigm does not apply. In any case, there are no obvious physical withdrawal symptoms during detoxification from cocaine (Cohen, 1984; Gold & Verebey, 1984; Gossop et al., 1995; Grinspoon & Balakar, 1985; Khantzian & Khantzian, 1984; Kleber & Gawin, 1984; Lago & Kosten, 1994; Mule, 1984; Siegel, 1984); rather, cocaine addicts typically complain of cocaine craving, mild dysphoria, anhedonia and anergia during the first few weeks following cessation of cocaine use (Kleber, 1995; Lago & Kosten, 1994). Human cocaine abusers describe positive drug effects such as ecstatic euphoria, confidence, energy, increased sociability, ego inflation, and aphrodisia as their reasons for taking cocaine (Gold & Verebey, 1984; Siegel, 1982; Spotts & Shontz, 1984; Washton & Gold, 1984), in addition to cocaine craving.

A variety of procedures have demonstrated that cocaine is the most reinforcing substance known in laboratory animals. When infrahumans were allowed to freely self-administer intravenous cocaine, their use of the drug escalated rapidly until they killed themselves within a few days (Bozarth & Wise, 1985; Deneau, Yanagita & Seevers, 1969). No other drug had such a rapid and dramatic effect on self-administration behavior, including heroin and amphetamines. Cocaine maintained higher response rates on a fixed ratio/timeout schedule than any dose of opiates in monkeys (Young & Woods, 1980), and in drug choice procedures, monkeys consistently chose cocaine over any dose of opiates (Balster & Schuster, 1977). Another method of assessing the relative reinforcement efficacy of different drugs is the "breaking point" procedure (Brady & Griffiths, 1983; Brady & Lukas, 1984; Griffiths, Bigelow & Liebson, 1978). Baseline drug-reinforced responding is established on a fixed ratio schedule, and then the ratio requirement is systematically increased until the animal stops responding - the so-called "breaking point." Cocaine produced higher breaking points than any other drug, including heroin or amphetamines. Monkeys continued responding for cocaine even when thousands of lever-presses were required for a single drug infusion. The fact that cocaine, a supposedly nonaddictive drug, proved far more reinforcing to laboratory animals than a "physically addictive" drug like heroin was at first a very surprising result. It is now clear that the reinforcing effects of drugs such as cocaine, opiates, or amphetamines all depend on their enhancement of dopamine activity in the mesolimbic dopamine system, the major "reward" pathway of the brain (Goeders & Smith, 1985; Roberts & Koob, 1982; Koob, 1992; Stewart, 1983; Wise & Rompre, 1989). Repeated episodes of cocaine reinforcement can rapidly establish a powerful habit, especially when the drug is taken via methods which provide an intense but brief effect such as "crack" smoking, which encourages repetitive dosing over relatively short periods of time.

Stewart (1983, 1984) described how a single noncontingent "priming" injection of cocaine reinstated cocaine-reinforced responding following extinction in rats. The priming effect was dose-dependent, such that a low priming dose led to short-term

reinstatement of lever-pressing, while a high priming dose elicited a considerably longer period of nonreinforced responding. De Wit and Stewart (1981) found that a tone that had been previously paired with cocaine infusions acted like a priming injection of cocaine itself to reinstate lever-pressing following extinction. Further, neutral stimuli paired with cocaine effects rapidly acquired secondary reinforcing properties (Stewart et al., 1984). Stewart et al.'s priming model can thus readily account for the craving induced by cocaine-related cues and the high relapse rates in cocaine addicts who seek treatment (Childress et al., 1988; O'Brien et al., 1992; Weiss, Griffin & Hufford, 1995; Withers et al., 1995), as well as the intense craving that is directly evoked by cocaine itself (de Wit, 1996; Van Dyck & Byck, 1982).

Similar considerations to those presented above for cocaine addiction argue against a physical dependence-based interpretation of tobacco dependence. The physical signs of nicotine withdrawal are subtle and chiefly reflect low arousal, including decrease in heart rate (Hughes, Higgins & Bickel, 1994), slowing of the EEG (Herning, Jones & Bachman, 1983; USDHHS, 1988), and decreased skin conductance orienting responses to novel stimuli (Lyvers, Boyd & Maltzman, 1988; Lyvers & Miyata, 1993). Indeed, the *absence* of obvious physical effects distinguishes tobacco withdrawal from the withdrawal syndromes of other addictive drugs (Hughes et al., 1994; Lyvers, Maltzman & Miyata, 1994). Craving for tobacco is usually considered the central sign of tobacco withdrawal (Kozlowski & Wilkinson, 1987; Tiffany, 1990; Wikler, 1980). Like other addictive drugs, nicotine stimulates dopamine release in the mesolimbic reward system (Balfour, 1994; Corrigal, Franklin, Coen & Clarke, 1992), is self-administered by laboratory animals under certain conditions (Slifer & Balster, 1985), and establishes place preferences (Fudala, Teoh & Iwamoto, 1985) which can be blocked by dopamine antagonists (Di Chiara, 1995). Thus tobacco dependence would seem to fit the currently popular positive reinforcement model of drug addiction (but see Balfour, 1994, for a critique of this view).
The Physical Basis of Addiction: Some Recent Alternatives to the Opiate Model

Given the overwhelming amount of evidence against withdrawal-relief as the major motive driving addictive behavior, some recent authors (e.g., Ray & Ksir, 1993) have concluded that all addictions represent "psychological" dependence, defined as positive reinforcement, even in the case of drugs which produce clear physical dependence (such as opiates or alcohol). Others (e.g., Begleiter & Kissin, 1996) continue to refer to "physical" and "psychological" types of drug dependence. But the distinction is misleading and perhaps should be abandoned. If addictive behavior results from enduring drug-induced changes in the physical brain, all drug addictions can be meaningfully regarded as reflecting a "physical" process irrespective of the presence or absence of autonomic withdrawal changes. The problem with the opiate model was its emphasis on autonomic signs of withdrawal and the false notion that addicts are profoundly determined to alleviate unpleasant peripheral symptoms. The opiate model was appealing because the idea that addicts "need" more drug in order to relieve distressing physical symptoms made their intense determination to obtain drugs seem understandable, a "rational" response to their withdrawal sickness. But the compulsive drug use of addicts may be no more "rational" than are the maladaptive repetitive behaviors exhibited by

patients with obsessive-compulsive disorder, which also appears to have a physical basis in the brain (Insel, 1992).

One recent approach has been to retain the basic idea of chronic drug-induced neuroadaptations leading to an aversive withdrawal state that demands relief, while at the same time deemphasizing the role of peripheral autonomic symptoms (e.g., Kleber, 1995).
This view is supported by evidence that the aversive stimulus properties of opiate withdrawal and the intensity of self-reported craving are poorly related to the severity of autonomic withdrawal signs (Di Chiara, 1995). During acute withdrawal from cocaine, amphetamines, or opiates, ESB reward thresholds are elevated and dopamine activity in the mesolimbic system is reduced compared to predrug baselines (Koob, 1992; Wise & Munn, 1995; Withers et al., 1995); the latter effect has been demonstrated during alcohol withdrawal as well (Diana, Pistis, Carboni, Gessa & Rossetti, 1993). Wise and Munn suggested that acute dopamine depletion underlies the dysphoria and anhedonia reported by addicts during early abstinence, but cautioned that evidence is lacking for a motivating role of dopamine depletion in addictive behavior. Indeed, as Di Chiara noted, an analogy for such withdrawal depression of the reward system is to be found in the acute action of neuroleptics, which block dopamine receptors and produce a *decrease* in motivated responding to incentive stimuli and which elicit extinction-like effects on drug-reinforced responding. Depression of the reward system should therefore inhibit drug use rather than provoke it, which is consistent with, for example, the cocaine addict's temporary loss of interest in cocaine during the "crash" phase (Self & Nestler, 1995). Cocaine craving, by contrast, is associated with *increased* levels of dopamine metabolites in abstinent addicts (Knoblich et al., 1992; Martin, Yeragani, Lodhi & Galloway, 1989). A recent PET scan study of abstinent cocaine addicts by Childress (unpublished, cited in Goleman, 1996) indicated that cocaine-related stimuli triggered activation of the mesolimbic dopamine system accompanied by intense cocaine craving.

The rejection of the withdrawal-relief model and the recent emphasis on primary reinforcing properties of drugs should not, however, lead to a redefinition of addiction as mere self-indulgence or "pleasure-seeking" (McAuliffe et al., 1985). While it is true that the substances considered to have the greatest addiction potential (cocaine and heroin) are the drugs which most consistently and powerfully evoke euphoric reactions, there are a few drugs which reliably produce euphoric effects without significant risk of addiction, such as marijuana and MDMA ("ecstasy") (Jones, 1992; Kirsch, 1986). The latter substances tend to be used on an episodic basis and rarely become the focus of compulsive behavior. Conversely, nicotine is now regarded as a highly addictive drug, as cigarette smoking appears to be as hard to give up as a cocaine or heroin habit (Kozlowski et al., 1989); yet the degree of euphoria induced by nicotine is not comparable to that elicited by cocaine or heroin, if indeed nicotine can be regarded as a euphoriant at all (Jarvis, 1994). But with the possible exception of nicotine, most addictive drugs are clearly euphorigenic at least during the early "honeymoon" phase of drug use. Cocaine reliably elicits self-reports of pleasure and a desire for more cocaine in human drug users and even in drug-naive persons (Mello, 1983a; Van Dyke & Byck,

1982), and heroin addicts and alcoholics tend to express positive expectancies about the anticipated effects of their drug of choice (McAuliffe & Gordon, 1974; Mello, 1983b). On the other hand, during binges cocaine addicts continue to take cocaine despite highly aversive acute effects such as anxiety, paranoia, agitation, panic attacks, and even convulsions (Spotts & Shontz, 1984; Withers et al., 1995). Similarly, infrahuman primates have been observed to self-administer intravenous cocaine despite adverse effects such as self-mutilation and seizures, to the point of overdose death (Deneau et al., 1969). When alcoholics were allowed to drink alcohol freely in a hospital setting, they described effects such as anxiety and depression despite their positive predrinking expectancies (Mello, 1983b), and social drinkers likewise reported alcohol-induced increases in fatigue, depression and confusion as assessed by the POMS (Ewing & McCarty, 1983). Certainly the nausea and vomiting commonly induced by high doses of alcohol or heroin must be a highly aversive experience, yet this seldom dissuades addicts from further drug-taking. Secondary negative effects of the drug habit must also be considered, such as disruption of family and other interpersonal relationships, loss of employment with associated financial problems, legal difficulties, and the risk of adverse health effects such as cirrhosis, lung cancer, cardiovascular disease, and withdrawal symptoms (depending on the drug). The negative aspects of a drug habit can turn previously enjoyable drug use into a nightmare, yet addicts often continue to use in spite of such effects. These considerations present a problem for theories which identify the positive reinforcing effects of addictive drugs with the elicitation of pleasureable affective states (e.g., Stewart et al., 1984). Moreover, recent evidence suggests that the pleasurable and reinforcing effects of addictive drugs are dissociable. Lamb et al. (1991) found that low doses of morphine which produced no subjective effects at all nevertheless reinforced responding for drug infusions in postaddicts, whereas placebo infusions did not do so. The desire for drug-induced euphoria probably accounts for the initiation and early maintenance of drug use, but not the compulsive behavior exhibited by addicts. Many addicts become motivated to quit when the drug's negative physiological effects and/or the external negative consequences of the habit become significant to them, by which time the intoxication produced by the drug may no longer be so pleasureable. Yet their initial attempts to quit often fail; they seem to have "lost control" of their drug-taking behavior. Their drug use is no longer rationally motivated, even to them. Indeed, addicts can be just as perplexed by their compulsive drug use as their nonaddict associates are (Washton & Tatarsky, 1984). Thus although addiction may have its beginnings in voluntary, controlled indulgence or self-medication of dysphoric moods, with time the habit seems to take on its own momentum, becoming relatively independent of its consequences and of the addict's verbalized intentions.

When addicts continue to use a drug despite obvious adverse effects, the fundamentally irrational nature of addiction is demonstrated. A nonaddict takes a drug such as cocaine for rational reasons, e.g., because he expects to obtain pleasureable, energizing effects from the drug. In an addict, by contrast, drug-taking seems to have become relatively "automatized," i.e., it no longer seems mediated by a conscious decision-making process (Tiffany, 1990). The drug habit has apparently taken on a life of its own, such that the subjective consequences of drug ingestion - good or bad - are no

longer important (Wade, 1995). According to Tiffany, relapse does not necessarily require conscious urges or craving, but may instead reflect spontaneous activation of the automatic, "subcortical" processes mediating drug use without concomitant activation of the nonautomatic, "cortical" processes devoted to maintaining abstinence (including the acknowledgement of a craving state). Thus negative affective events may lead to relapse not because they elicit craving due to their resemblance to withdrawal states, but because they prompt attempts at coping which reduce the nonautomatic cognitive resources devoted to resisting the automatic tendency of drug use. Supporting this view, recent studies have reported no relationship between craving and relapse in cocaine addicts (Weiss, Griffin & Hufford, 1995) and cigarette smokers (Wiseman & McMillan, 1995). Craving was only rarely chosen by relapsed alcoholics and cocaine addicts as the cause of their relapse in a recent study by Miller and Gold (1994); reasons given for relapse were heterogenous and included depression, happiness, anxiety, and social pressure, consistent with many other studies of relapse factors (Cummings, Gordon & Marlatt, 1980; Litman, Stapleton, Oppenheim, Peleg & Jackson, 1983; O'Brien et al., 1984; Orford, 1985). Miller and Gold suggested that most addicts' explanations of their relapses reflect post hoc rationalization, hence the heterogeneity of their responses. Interestingly, the cocaine addicts in Miller and Gold's study most often attributed their relapse to "impulsive action with no known cause," consistent with Tiffany's view of addiction as relatively unconscious, irrational, "automatic" drug-taking behavior.

Addictive drug-taking has a "driven" quality, exhibiting parallels with obsessive-compulsive disorder (OCD). According to Modell and associates (Modell & Mountz, 1995; Modell et al., 1993), OCD and alcoholism similarly involve subcortical dopamine circuits, and chronic alcohol-induced changes in the brain (such as dopamine receptor supersensitivity) are the basis of an enhanced dopaminergic response to alcohol and alcohol cues that manifests behaviorally as alcoholic craving and loss of control. This view is quite compatible with the incentive-sensitization theory of addiction recently proposed by Robinson and Berridge (1993). In the latter theory, repeated drug activation of brain dopamine systems leads to an enduring sensitization of these systems, which are concerned not with pleasure per se but rather with assigning motivational significance to external stimuli. Thus as the drug user continues to take an addictive drug, drug "liking" or pleasure does not necessarily increase and may even decrease, while drug "wanting" increases to the point where it becomes an irrational craving or overpowering desire. Through associative learning, drug-related cues come to evoke dopamine release, strong ORs and intense craving. As Robinson and Berridge put it,

> If drug use continues, dopamine systems become progressively more sensitized. With each repetition greater and greater incentive salience is attibuted to drug-related stimuli and the associative pairing of drug-related stimuli with the intense activation of dopamine systems produced by drugs leads to an increasing focus of salience attributed upon just these stimuli. Thus "wanting" is gradually transformed into craving, drugs become craved to the relative exclusion of all else, and drug-associated stimuli elicit this craving independent of any pleasure they produce (p. 267).

Robinson and Berridge amassed a considerable amount of evidence supporting their theory, which seems capable of accounting for many phenomena of addiction. For example, the enduring susceptibility of postaddicts to relapse can be explained by the long-lasting and possibly even permanent sensitization of dopamine systems. Such sensitization may also explain the tendency of postaddicts to gain weight or to engage in substitute compulsive behaviors (Vaillant, 1992), as dopamine systems also mediate motivational responses to various nondrug incentives. Persistent sensitization of cocaine- or amphetamine-induced dopamine release in the nucleus accumbens as a result of chronic drug exposure is now a well-established phenomenon (Self & Nestler, 1995). Further, Brauer and de Wit's (1995) recent finding that the pleasureable effects of amphetamine were not blocked by dopamine antagonists supports Robinson and Berridge's hypothesis that the pleasureable effects of addictive drugs are not specifically mediated by brain dopamine systems, in contrast to their incentive-motivational effects. The incentive-sensitization theory thus seems an especially promising physiological approach to addiction, but the crucial causal link between sensitization of dopamine systems and addictive behavior has yet to be demonstrated in human addicts.

In conclusion, as it increasingly appears that the constellation of pathological behaviors defining drug addiction may be traceable to enduring physical changes in the brain, the popular notion that drug addiction represents a "physical disease" may yet be vindicated despite the failure of the opiate model. The physical nature of such a disease would not be found in peripheral autonomic symptoms, which are variable in their manifestation, but in specific brain circuits that are affected similarly by all addictive drugs.

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